I. REMARKS

Preliminary Remarks

Claims 7 to 9, 12 to 19, and 29 to 43 are pending of which claims 7 and 8 are independent. No claims are amended, withdrawn, canceled, or added.

This response is filed within the statutory period for response and is accompanied by a petition for a one-month extension of time, three pages from *The Journal of the American Medical Society* (*JAMA* **282(3)**, 233 – 235, 1999), and a Credit Card Payment Form (PTO-2038) for payment of the required fees. The applicants respectfully request reconsideration and allowance of the present application.

Patentability Remarks

Rejections under 35 U.S.C. § 102 –

Claims 7, 31, and 34 were rejected under 35 U.S.C. §102(b) as being anticipated by Heymsfield *et al.* (*JAMA* **280(18)**, 1596 – 1600, 1998). The applicants respectfully traverse in view of the succeeding remarks.

Contrary to the examiner's statement in the pending official action, the study in Heymsfield *et al.* was conducted using highly purified hydroxycitric acid (HCA) only. Heymsfield *et al.* obtained this material from the current inventors and the inventors' extraction method does not allow for "impurities" such as garcinol. The Heymsfield *et al.* study supposedly showed no clinical effects of the HCA on weight loss and body composition as compared to a placebo. The applicants enclose a reference from JAMA containing with their rebuttal (along with two others and a reply from Heymsfield *et al.*) to the results of Heymsfield *et al.* The applicants respectfully request the examiner to note that all rebuttals and the reply Heymsfield *et al.* refer to HCA only.

In contrast, in the current application the applicants compared the HCA used by Heymsfield *et al.* to the composition of the invention, namely HCA and garcinol. The applicants found that the claimed composition (*i.e.*, HCA and garcinol) is significantly better to HCA alone. Therefore, the applicants respectfully submit that claims 7, 31, and 34 cannot be anticipated by Heymsfield *et al.* and respectfully request withdrawal of this rejection.

Claim 7 was rejected under 35 U.S.C. §102(b) as being anticipated by JP 10-265397. The applicants respectfully traverse in view of the succeeding remarks.

Garcinia fruit as claimed by JP 10-265397 for the treatment of obesity has totally different composition from the HCA/garcinol claimed. In particular, there are insufficient amounts of HCA or garcinol in JP 10-265397 to achieve the fat catabolism as presently claimed.

The present invention is a unique composition of HCA and garcinol not occurring in nature or in any other garcinia or HCA products. The HCA in the present invention is isolated by a separate method from the isolation of garcinol (note that the extraction process used for HCA removes "impurities" such as garcinol), and then the two products are combined. The efficacy of the composition of the invention is supported by pre-clinical and clinical studies as described in the patent application (see, for example, pages 10 to 12).

The applicants respectfully submit that claim 7 is not anticipated by JP 10-265397 and respectfully request withdrawal of this rejection.

II. CONCLUSION

In view of the remarks above, the applicants respectfully submit that this application is in condition for allowance and request favorable action thereon.

In the event that this response is not timely filed, the applicants hereby petition for an appropriate extension of time. The fee for this extension, along with any additional fees that are required with respect to this response, may be charged to Deposit Account No. 01-2300, referencing Attorney Docket No. 108064-00051.

Respectfully submitted,

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The manipulative techniques used in this study reflected the majority of practices and teaching methods. Our practitioner used a variety of techniques, indicated by the "gold standard" of palpation and applied using years of accumulated experience. It is unlikely that the choice matters, however, since most therapists use strikingly similar techniques, especially in the cervical spine. Moreover, there is no indication that one technique that gaps the joint is superior to another, although most chiropractors would agree that gapping the joint is important. We remind readers that any adjustment, applied injudiciously, can provoke pain and other symptoms.

The possibility of a type II error always exists; we minimized ours using a statistical power of 90% to detect a 1-hour difference in daily headache hours. But our point here, really, is that even if a statistically significant treatment effect is found in a randomized controlled trial, that treatment effect may not be large enough to be of practical clinical interest (ie, "of clinical significance"). For example, in our research, a larger sample size may have shown a statistically significantly reduced analgesic intake. However, even at the extremes of our confidence intervals, this would not have amounted to more than a half dose of the analgesics.

Headache diagnosis is fraught with pitfalls, and tension and cervicogenic headache presentations often overlap. In our experience, many field practitioners are not aware of the distinctions between these specific diagnostic categories, yielding statements like " . . . ETTHs resulting from cervical joint dysfunction." Headaches resulting from cervical joint dysfunction are *cervicogenic* headaches. This is important because this group of patients responds remarkably well to manipulation. Our combined clinical and scientific experience suggests that if a manipulation treatment helped a tension-type headache, it probably was a misdiagnosed cervicogenic headache.[1]

We suggest that practitioners learn to differentiate cervicogenic and tension-type headaches, since they clearly demand different treatments, and the 2 types together amount to about 80% of all headache cases.[2,3] We also suggest that practitioners apply the information contained in research articles judiciously and without emotion, and consider, when possible, the intent of the authors.

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1. Nilsson N, Christensen HW, Hartvigsen J. The effect of spinal manipulation in the treatment of cervicogenic headache. *J Manipulative Physiol Ther.* 1997;20:326-330.
2. Nilsson N. The prevalence of cervicogenic headache in a random population sample of 20-59 year olds. *Spine.* 1995;20:1884-1888.
3. Rasmussen BK. Epidemiology of headache. *Cephalalgia.* 1995;15:45-68.

Garcinia cambogia for Weight Loss

To the Editor: In their study evaluating the weight-loss potential of (-)hydroxycitric acid (HCA) derived from *Garcinia cambogia*, Dr Heymsfield and colleagues[1] cite our HCA work. We wish to give a counterpoint to the conclusion expressed by the authors.

Based on their single clinical study, Heymsfield et al state that "These observations ... do not support a role as currently prescribed for the widely used herb *G cambogia* as a facilitator of weight loss." Aside from this strong statement, which contradicts the positive results reported in several earlier HCA clinical studies, the design of the trial indicates that the authors took little advantage of previously reported experiences involving HCA.[2-4] In their own preclinical research, they report a prerequisite that suggests for HCA to effectively inhibit fat formation and body weight it needs to be administered with a simple carbohydrate-rich (lipogenic) diet.[5]

The study in question[1] coadministered HCA with a high-fiber diet. This issue of a carbohydrate-rich diet vs a high-fiber diet was not mentioned by Heymsfield et al. Also lacking was mention of the fact that a high-fiber diet was not advocated in our previous HCA trials.[2-4]

The use of a high-fiber diet in combination with HCA may reduce gastrointestinal absorption of HCA, since high-fiber diets may reduce absorption of many nutrients and micronutrients. This issue becomes critical with HCA because its reported efficacy in inhibiting the intracellular enzyme adenosine triphosphate(ATP)–citrate-lyase depends entirely on the presence of HCA inside the target cell.

The significance of HCA availability in the cytosol of a target cell for inhibiting lipid synthesis or ATP–citrate-lyase was recently confirmed in 2 separate studies performed by Joanne Kelleher, PhD, at George Washington University (oral communication, November 24, 1998) and Joel Melnick, MD, at Northwestern University Medical School.[6] The compound used in both of these studies was the same commercially available HCA used in the study by Heymsfield et al.

In view of the shortcomings of the study discussed above, the statement on HCA's lack of efficacy is unsupported, particularly in the absence of proof that HCA was absorbed from the gastrointestinal tract.

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Disclosure. Sabinsa Corporation is a manufacturer of hydroxycitric acid.

1. Heymsfield SB, Allison DB, Vasselli JR, Pietrobelli A, Greenfield D, Nunez C. *Garcinia cambogia* (hydroxycitric acid) as a potential antiobesity agent: a randomized controlled trial. *JAMA.* 1998;280:1596-1600.
2. Conte AA. A non-prescription alternative in weight reduction therapy. *Am J Bariatr Med.* Summer 1993:17-19.
3. Conte AA. The effects of (-)-hydroxycitrate and chromium (GTF) on obesity. *J Am Coll Nutr.* 1994;13:535. Abstract 60.
4. Badmaev V, Majeed M. Open field, physician controlled, clinical evaluation of botanical weight loss formula Citrin. Presented at: Nutracon 1995: Nutraceuticals, Dietary Supplements and Functional Foods; July 11, 1995; Las Vegas, Nev.
5. Vasselli JR, Shane E, Boozer CN, Heymsfield SB. *Garcinia cambogia* extract inhibits body weight gain via increased energy expenditure (EE) in rats. *FASEB J.* 1998;12:A506.
6. Puttaparthi K, Rogers T, Elshourbagy NA, Levi M, Melnick JZ. Renal ATP citrate lyase (ATP CL) protein localizes throughout the nephron and increases only in the

proximal tubule with chronic metabolic acidosis (CMA). Abstract presented at Pediatric Academic Societies' 1999 Annual Meeting. May 2, 1999; San Francisco, Calif.

To the Editor: Dr Heymsfield and colleagues[1] reported that "*Garcinia cambogia* failed to produce significant weight loss and fat mass loss [in humans] beyond that observed with a placebo," while previous reports indicate that *G cambogia* HCA decreases appetite, reduces food intake, and inhibits fat synthesis in animals,[2,3] and reduces body weight, triglycerides, and cholesterol levels in humans.[4] Why the disparity?

First, the low-energy, 5040-kJ diet used in the study by Heymsfield et al negated the utility of HCA. This agent is a potent competitive inhibitor of ATP–citrate-lyase,[3] an enzyme that converts citrate (a product of the Krebs citric acid cycle derived from carbohydrate metabolism) into acetyl–coenzyme A (CoA), the primary building block of fatty acid and cholesterol synthesis. However, the conversion of citrate to acetyl-CoA by ATP–citrate-lyase occurs only when the rate of glycolysis exceeds the energy requirements of the body.

If the body's energy needs are not met, the Krebs cycle converts carbohydrate calories into ATP for energy rather than citrate for fatty acid synthesis. Thus, a low-energy diet that does not exceed the energy requirements of the body would not provide the substrate (ie, citrate) necessary for fatty acid synthesis and thus would fail to demonstrate HCA's ability to inhibit fat production from excess carbohydrate consumption.

Second, HCA inhibits appetite and reduces food intake administered ad libitum in animals.[2] However, the study by Heymsfield et al failed to evaluate HCA's ability to reduce food intake by virtue of its energy-restricted protocol. Although diet compliance was not quantitatively monitored during the study, subjective indices of patient compliance and feelings of satiety also were not assessed. In a similar study, Ramos et al[4] reported that subjects taking HCA adhered to a recommended low-energy diet better than subjects receiving a placebo.

Third, the dose of HCA used in the study was low compared with that used in earlier successful animal trials.[3] Bioavailability also may have been reduced. Excessive levels of calcium (used to stabilize the HCA molecule), high levels of naturally occurring pectin, and low solubility in water, factors that can reduce bioavailability, are know to exist in many, but not all, commercial HCA extracts. Since blood levels of HCA were not assessed, it is possible that the extract selected for this study had poor bioavailability and thus failed to deliver an effective dose.

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1. Heymsfield SB, Allison DB, Vasselli JR, Pietrobelli A, Greenfield D, Nunez C. *Garcinia cambogia* (hydroxycitric acid) as a potential antiobesity agent: a randomized controlled trial. *JAMA*. 1998;280:1596-1600.
2. Sullivan AC, Triscari J, Hamilton JG, Miller ON. Effect of (-)-hydroxycitrate upon the accumulation of lipid in the rat, II: appetite. *Lipids*. 1974;9:129-134.
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To the Editor: According to Dr Heymsfield and colleagues,[1] "*Garcinia cambogia* [HCA] failed to produce significant weight loss and fat mass loss beyond that observed with a placebo"; "studies in humans are contradictory"; and ". . . at least 14 separate hydroxycitric acid–containing products are presently sold over-the-counter to consumers."

The main active component in the herbal extract of *Garcinia* compound is HCA. The earliest research, conducted in the 1970s, into the antiobesity effects of HCA was conducted by Hoffmann-La Roche Pharmaceuticals. Studies have shown the ability of HCA to inhibit the actions of citrate cleavage enzyme, suppress fatty acid synthesis, increase hepatic glycogen synthesis, suppress food intake, increase energy expenditure, curb appetite, reduce plasmatic cholesterol levels, and inhibit fat synthesis from excess carbohydrate calories.[2,3] The properties of *Garcinia* extract have been confirmed by clinical trials published in peer-reviewed literature.[2-4]

In the study by Heymsfield et al,[1] only the amount of HCA, and not the chemical composition of the extract, was verified by chemical analysis. The bioavailability of the HCA product tested was not assessed, a quality factor that might significantly affect the results because many HCA products available on the market today have low bioavailability.

Excess calcium, common among many HCA products, reduces solubility and hinders bioavailability. Calcium-type powder is stable but not ideal for food products due to its insolubility in water.[5] However, a compound complexed with calcium and potassium is nearly 100% soluble and creates a pH level that is favorable for maximum gastrointestinal absorption, 2 critical components of bioavailability. A soluble *Garcinia* powder and liquid extract containing a lactone form of HCA was compared with a calcium-type *Garcinia* powder administered in food to rats, and the liquid extract was proven more effective.[5]

Another problem of the study centers on the restricted diet used. Because all patients lost weight, including the placebo group, the study design eliminated any opportunity to demonstrate that HCA curbs appetite, reduces food intake, and inhibits fat synthesis in an unrestricted diet as the conversion of citrate into acetyl-CoA occurs only when the energy consumed exceed the energy requirements of the body.

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1. Heymsfield SB, Allison DB, Vasselli JR, Pietrobelli A, Greenfield D, Nunez C. *Garcinia cambogia* (hydroxycitric acid) as a potential antiobesity agent: a randomized controlled trial. *JAMA*. 1998;280:1596-1600.
2. Ramos RR, Saenz FJ, Alarcon A. Extract of *Garcinia cambogia* in the control of obesity [in Spanish]. *Invest Med Intern*. 1996;22:97-100.
3. Rothacker DQ, Waitman BE. Effectiveness of a *Garcinia cambogia* and natural caffeine combination in weight loss: a double-blind placebo-controlled pilot study. *Int J Obes*. 1997;21(suppl 2):53.
4. Girola M, De Bernardi M, Contos S, et al. Dose effect in lipid-lowering activity of a new dietary integrator (chitosan, *Garcinia cambogia* extract, and chrome). *Acta Toxicol Ther*. 1996;17:25-40.
5. Sawada H, Tomi H, Tamura K, et al. Effects of liquid *Garcinia* extract and soluble *Garcinia* powder on body weight change: a possible material for suppressing fat accumulation. *Nihon Yukagaku Kaishi*. 1997;46:1467-1474.

In Reply: The increasing prevalence of obesity combined with the low efficacy of conventional treatments led us to examine the weight-loss effects of *G cambogia*, a natural source of the citrate-lyase enzyme inhibitor HCA. Our double-blind, randomized controlled trial was designed from the consumer's perspective: we administered either a placebo or widely available *G cambogia* preparation in suggested amounts along with dietary recommendations typical of that provided in package inserts.[1] Our negative observations in the first adequately controlled and reported trial of this widely used herbal agent prompted several letters from readers.

The first group of issues raised by the respondents involves the low-fat, high-fiber hypocaloric diet recommended to our subjects in both placebo and active herb groups. Dr Badmaev and colleagues hypothesize that a high fiber intake may lead to gastrointestinal HCA binding with subsequent loss of enzyme inhibitor bioavailability. Dr Schaller's concern is that the citrate cleavage enzyme is relatively inactive when the subject is in negative energy balance, as would occur with ingestion of a low-energy diet. Drs Firenzuoli and Gori also express a similar concern regarding use of *G cambogia* with an energy "restricted" diet. These suggestions provide a potential theoretical basis for why the product tested in our study was "ineffective as prescribed." Nevertheless, our investigation was based on typical product diet plans[2] and similar to that prescribed in the *Garcinia* studies by Conte[3] and Badmaev et al.[4]

The second important group of comments extends Badmaev and colleagues' bioavailability concern. Firenzuoli and Gori report that water solubility, and thus gastrointestinal absorption of HCA, depends on factors such as degree of calcium and potassium acid complexing and acid vs lactone forms. Schaller also invokes the low-bioavailability hypothesis by again suggesting that fibers such as pectin and calcium stabilization may conspire to reduce HCA absorption. Administered dosage, as mentioned by Schaller, was lower than that used in earlier successful animal experiments. Our dosage of HCA was, however, almost identical to that used in most commercial preparations, in Conte's human study,[3] and in Badmaev and Majeed's study.[4]

As potential consumers, we may ask why it remains uncertain that HCA derived from an over-the-counter product reaches its cellular destination in amounts adequate to actively inhibit citrate cleavage enzyme. Why are diet plans suggested to consumers that may render *Garcinia*'s active agent nonabsorbable or inadvertently switch off the target citrate cleavage enzyme? Critical tests pinpointing each step in HCA uptake, distribution, and biological effects in humans are long overdue.

The need now exists to build, piece by piece, a strong series of human studies that establish if any *G cambogia* preparations can be added to the list of safe and effective weight-loss or weight-gain–prevention agents. Until this scientific foundation is established, consumers must rely on appropriately designed studies, such as ours, to judge if herbal weight-loss products such as the evaluated *G cambogia* preparation offer effective therapy beyond that of well-established diet and exercise measures.

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1. Thermogenic Ultra Lean [package insert]. Herbal weight loss plan with *Garcinia cambogia*. Salt Lake City, Utah: Great American Nutrition; 1998.
2. Committee for Proprietary Medicinal Products. *Note for Guidance on Clinical Investigation of Drugs Used in Weight Control*. London, UK: The European Agency for the Evaluation of Medical Products; 1997.
3. Conte AA. A non-prescription alternative in weight reduction therapy. *Am J Bariatr Med*. Summer 1993:17-19.
4. Badmaev V, Majeed M. Open field, physician controlled, clinical evaluation of botanical weight loss formula Citrin. Presented at: Nutracon 1995: Nutriceuticals, Dietary Supplements and Functional Foods; July 11, 1995; Las Vegas, Nev.

Managed Care Market Share, Fee-for-Service Medicare, and Information Theory

To the Editor: In examining the association between managed care market share and health care expenditures for fee-for-service Medicare patients, Dr Baker[1] finds a significant inverse association between systemwide health maintenance organization (HMO) market share and Medicare fee-for-service expenditures. Baker suggests that HMO activity may influence fee-for-service expenditures through 3 factors: availability of medical infrastructure and services, physicians' adoption of neighboring physicians' behaviors, and changes in traditionally nonmanaged care insurers as response to the presence of managed care. Furthermore, Baker theorizes that lower service prices contribute little to decreased overall costs.

We believe that information theory provides an alternative, possibly complementary, explanation. Information theory postulates that physicians' recommendations are, at least in part, a function of the physician utility ("happiness") function, the severity of the patient's illness, and the level of knowledge of the patient about his or her illness and its appropriate treatment.[2] Information theory further postulates that increases in the knowledge level of patients about appropriate treatment will lead to lower tolerance in practice variations, even if only a few patients increase their knowledge. Also, this theory predicts that policies aimed at reducing practice variations will encourage search among patients for those whose practices are considered "best" at the time.

We believe that managed care organizations may be acting as "patients" with increased levels of knowledge. Health maintenance organizations could be discouraging practice variations directly by the mechanisms suggested by Baker and also by stimulating the general use of practice guidelines. Managed care organizations could also indirectly favor decreased practice variations by offering standards of care that may be, at least at times, more cost-effective for the patients. Commu-